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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,445	01/24/2001	Peter J. Houghton	OC01128K	2381

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PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
DELACROIX MUIRHEI, CYBILLE	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,445	HOUGHTON, PETER J.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/27/01;05/31/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Claims 1-26 are presented for prosecution on the merits.

Information Disclosure Statement(s)

Applicant's Information Disclosure statements received June 27, 2001 and May 31, 2002 have been considered. Please refer to Applicant's copies of the 1449 submitted herewith.

Specification

The use of the trademark Haldol®, Benadryl®, etc. has been noted in this application. Please see page 6, lines 15-16. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Objection(s)

1. Claim 25 is objected to because of the following informalities: in claim 25, line 2, there should be a **-- .** – and the end of the claim. Appropriate correction is required.

Claim Rejection(s)—35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling the treatment of neuroblastoma, glioblastoma and rhabdomyosarcoma, does not reasonably provide enablement for the treatment of all types of cancer using the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

2. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to a method for treating a human patient suffering from cancer by administering an effective amount of temozolomide and irinotecan.

(2) The state of the prior art

With respect to the term "cancer", this a broad term which encompasses numerous forms of cancerous diseases, each involving different types of tissues and

organs. As recognized in the art, many different antineoplastic drugs are used to treat a variety of cancers. Please see Goodman & Gilman's pages 1227-1229.

Additionally, Burton et al. (relied upon in the following rejection) teach that not all patients with malignant gliomas respond equally to chemotherapy. So, if such unpredictability exists in patients suffering from a specific type of cancer, i.e. malignant gliomas, one may infer that not all patients suffering from different types of cancer involving different tissues would respond equally to the administration of temozolomide and irinoecan.

(3) The relative skill of those in the art

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical and chemical art is high.

(5) The breadth of the claims

The claims are very broad and encompass treatment of numerous types of cancer by administering the claimed compounds.

(6) The amount of direction or guidance presented

Applicant's specification does not provide guidance for the treatment of all types of cancers using temozolomide and irinotecan. The specification provides no guidance to enable one of ordinary skill in the art to use the invention commensurate in scope with the claims, which, as stated above, are broad and encompass numerous cancerous diseases. Applicant has not set forth a representative number of examples of cancers capable of being treated by the administration of temozolomide and irinotecan.

Applicant's Examples describing the activity of temozolomide and irinotecan against neuroblastoma, glioblastoma and rhabdomyosarcoma cancer models in mice are not representative of the huge scope of cancers encompassed by the claims.

(7) The presence or absence of working examples

The only working examples in the specification involve studying the activity of temozolomide and irinotecan against neuroblastoma, glioblastoma and rhabdomyosarcoma human xenograft cancer models in immune deprived mice, followed by a description of a clinical study design for treating cancer patients.

(8) The quantity of experimentation necessary

Since (1) the art establishes that there are numerous forms of cancer treatable by many different anti-neoplastic agents and that no one compound is effective against all types of cancer; (2) since the claims are broad and require the treatment of numerous types of cancer, (3) since patient response to chemotherapy is unpredictable (as suggested by the Burton et al. article), and (4) since the specification does not provide guidance or a representative number of working examples, which would reasonably correlate to the broad scope of protection sought by the claims, one of ordinary skill in the art would be burdened with undue experimentation to determine which of the cancerous disorders encompassed by the claims would be treatable using the combination of temozolomide and irinotecan.

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al. and Ragab 6,346,524 (submitted by Applicant).

Burton et al. discuss new chemotherpay option for patients suffering from malignant gliomas. Two new drugs, temozolomide and irinotecan have shown promise in the treatment of patients who have malignant gliomas. Temozolomide is an oral phaemaceutical agent that has shown good responses in patients during Phase II studies. Please see page 159, Cytotoxic chemotherapy, first full paragraph.

Irinotecan is an intravenous drug that has previously been used in the treatment of colon cancer. Burton et al. teach that, as a single agent, irinotecan demonstrated a good response with malignant gliomas. In one study 60 patients with recurrent malignant gliomas were treated with a 125 mg/m^2 dose weekly for 4 weeks, followed by a 2 week period of rest. Please see page 159, Cytotoxic chemotherapy, second full paragraph.

Ragab disclose a method of treating a patient suffering from cancer by administering an effective amount (40-150 mg/m^2/day) for a dosing period of from 5 to 25 days. Ragab also discloses that treatment cycles may continue for as long as needed to cure or eliminate the cancer that is being treated. Please see the abstract; col. 2, lines 31-47.

Burton and Ragab do not specifically disclose treatment methods involving a combination of temozolomide and irinotecan. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Burton et al. and Ragab to treat malignant gliomas using a combination of temozolomide and irinotecan because one of ordinary skill in the art would reasonably expect the additive effect of temozolomide and irinotecan to be effective in treating malignant gliomas. Such a modification would have been motivated by the reasonable expectation that the combination of the two chemotherapeutic drugs would effectively treat patients suffering from malignant gliomas.

Moreover, modification to specifically combine temozolomide and irinotecan both of which are known to be useful for the same purpose, would have been obvious to one of ordinary skill in the art in view of the fact that the courts have held that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose" Kindly refer to In re Susi, 169 USPQ 423, 426 (CCPA 1971); In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

With respect to the claimed dosage amounts of temozolomide and irinotecan, since the anti-tumor effect of these drugs is dependent upon dosage amounts, it would have been obvious to one of ordinary skill in the art to further modify the dosage amounts in the prior art such that temozolomide and irinotecan are administered in an amount that is effective to optimize treatment of malignant gliomas.

Finally, with respect to the claimed dosing schedule, since Burton et al. establish a preferred dosing schedule at least for irinotecan, it would have been obvious to one of ordinary skill in the art to further modify dosing schedules such that the overall combination of temozolomide and irinotecan is effective in treating the patients suffering from malignant gliomas.

4. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Burton et al., in view of Ragab, supra.

Burton as applied above.

Ragab as applied above. In addition, Ragab discloses a medical kit containing temozolomide and printed instructions for administering the drug to a cancer patient. Please see the abstract; col. 3, lines 19-30

Burton et al. and Ragab do not specifically disclose a medical kit containing a combination of temozolomide and irinotecan along with printed instructions for administration to a cancer patient.

However, modification to specifically combine temozolomide and irinotecan both of which are known to be useful for the same purpose, would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the fact that the

courts have held that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose" Kindly refer to In re Susi, 169 USPQ 423, 426 (CCPA 1971); In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

With respect to the printed instructions for use, since the printed instructions relate to the intended use of the product and do not further define the product structurally or chemically it does render the claimed combination unobvious. Furthermore, the court in In re Ngai et al. states that "where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." Please see In re Ngai et al., 03-1524 (CAFC 2004)(affirming In re Gulack, 703 F.2d 1381 (Fed. Cir. 1983)). In this case, the printed instructions does not depend on the medical kit and the medical kit does not depend on the printed instructions. The ultimate function of the medical kit does not rely on the instructions but on the active pharmaceutical agents, i.e. temozolomide and irinotecan.

Conclusion

Claims 1-26 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cybille Delacroix-Muirheid whose telephone number is 571-272-0572. The examiner can normally be reached on Mon-Fri from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached at 571-272-0584. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM

June 10, 2004

Cybille Delacroix-Muirheid
Patent Examiner Group 1600